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Kakuchi-Fujimoto Disease Associated with Autoimmune Hepatitis and Systemic Lupus Erythematosus

Mithu Maheswaranathan, M.D.[1] and Melissa Cunningham, M.D., Ph.D.[2]

From the Department of Internal Medicine[1] and Division of Rheumatology[2], Medical University of South Carolina, Charleston, SC, USA

ABSTRACT

Systemic lupus erythematosus (SLE) is often associated with various systemic manifestations, from peripheral cytopenias to renal involvement or neuropsychiatric symptoms. Here, we present a patient in whom the cause of fever and altered mental status was unknown despite repeated lumbar punctures, but later became elucidated following the development of rash and lymphadenopathy with subsequent biopsies. This case demonstrates a unique presentation of Kakuchi-Fujimoto Disease, a necrotizing lymphadenitis manifesting in association with SLE and autoimmune hepatitis. Further, this case illustrates the proclivity of autoimmune disorders to occur concurrently.

Key Words:

systemic lupus erythematosus, lymphadenopathy, autoimmune hepatitis, Kakuchi-Fujimoto Disease, necrotizing lymphadenitis, encephalopathy

Author contributions:

Mithu Maheswaranathan – drafting of the manuscript; critical revision of the manuscript for important intellectual content;
Melissa Cunningham – drafting of the manuscript; critical revision of the manuscript for important intellectual content, supervisory

***Correspondence to Author:**
Mithu Maheswaranathan, MD
Department of Internal Medicine
Medical University of South Carolina
165 Ashley Avenue MSC 917
Charleston, SC 29425
Telephone: 803-493-7057
Fax: 843-792-9223

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Case Presentation

A 34-year-old African American male developed fever, altered mental status and hallucinations. He had been hospitalized twice with similar complaints and negative workup. His neuroimaging including head CT and brain MRI were normal. CSF cultures and viral studies returned negative, however lumbar punctures did demonstrate signs of inflammation with lymphocytic pleocytosis (CSF WBC 13 and 41) and mildly elevated protein. He received antimicrobials (vancomycin, ceftriaxone, acyclovir) until CSF cultures returned negative and was felt to have a viral meningoencephalitis. He was discharged but presented again similarly with fever and altered mental status, but now also with new rash and diffuse lymphadenopathy.

The patient's past medical history was remarkable for depression, history of gunshot wound, R distal radius fracture s/p ORIF, and C2/C4 fracture following ATV accident. Social history was remarkable for polysubstance abuse including marijuana, alcohol and smoking. He did not use other illicit drugs. His only medication had been Zoloft in the past for depression, which he stopped taking prior to presentation.

On physical exam, the patient was diaphoretic and disoriented. His temperature was 36.3^{o}C, blood pressure 114/74 mm Hg, heart rate 94 bpm, respiratory rate 22, and oxygen saturation 97% on room air. His skin felt warm. He had erythematous nodular lesions over the face, scalp, shoulders and upper trunk. He also had diffuse cervical lymphadenopathy and palpable inguinal adenopathy.

Laboratory data were notable for normocytic anemia (hemoglobin 9.7 and hematocrit 28%) and white blood cell count 5470/mm^3 with peripheral eosinophilia (9.6%), with normal platelets 241000/mm^3. His anemia was likely anemia of chronic disease given elevated ferritin (13,164 ng/mL) with normal iron (48), percent saturation Fe/TIBC (32%) and haptoglobin (205 mg/dL). He developed subsequent mild leukopenia during hospitalization (nadir 3330/mm^3). Liver function tests were remarkable for transaminitis (AST 130 U/L, ALT 98 U/L) as well as a protein gap with total protein 8.4 g/dL and albumin 2.9 g/dL. Liver synthetic function was normal with INR 0.99. Gamma-glutamyl transferase (GGT) was elevated at 142 U/L, suggesting the transaminitis was hepatic in origin. Creatine kinase was elevated at 962 U/L but normalized during the hospitalization, and the myositis antibody panel was negative. Viral serologies including HIV and hepatitis B and C were all negative. Other viral testing for Bartonella henselae, Toxoplasma gondii and West Nile virus returned negative. BMP was notable for hyponatremia (sodium 130 mmol/L) but otherwise within normal limits. Inflammatory markers were elevated including erythrocyte sedimentation rate (ESR) >100 mm/hr (ref: 0-15) and CRP 1.63 mg/dL (ref: 0-1). Urinalysis was unremarkable with no active urinary sediment.

Biopsy of the rash on the left arm demonstrated an interface dermatitis with necrotizing vasculitis on pathology (Figure 1). An excisional lymph node biopsy was also performed (Figure 2) which demonstrated signs of Kakuchi-Fujimoto Disease, a necrotizing lymphadenitis which can occur independently from, or associated with, systemic lupus erythematosus. Autoimmune serologies were suggestive of SLE given ANA positivity (at 1:160 titer, speckled pattern) and positive anti-Smith antibody (1.4). Complements (C3 and C4) were within normal limits and dsDNA antibody returned negative. Rheumatoid factor was negative. Our patient had a clinical diagnosis of systemic lupus erythematosus suggested by meeting at least 4 of the 17 SLICC (Systemic Lupus International Collaborating Clinics) criteria: +ANA, +anti-Smith, leukopenia and neurologic manifestations. CT angiography demonstrated a small, isolated peripheral pulmonary embolus without signs of right heart strain and the patient was started on apixaban for anticoagulation. Given the pulmonary embolus

and the proclivity of antiphospholipid antibody syndrome (APLS) associated with autoimmune conditions, APLS serologies (beta 2 glycoprotein IgG and IgM, anticardiolipin IgG and IgM, and dilute Russell viper venom time or DRVVT) were obtained and returned negative. CSF studies for oligoclonal bands, antineuronal antibodies and anti-ribosomal p antibodies from CSF to evaluate for CNS lupus were also recommended but ultimately not obtained. Serum ribosomal p antibody IgG returned negative, a serology that can be positive in patients with CNS lupus. His mental status changes resolved spontaneously during the admission.

Following discharge, additional serologies returned suggestive of possible autoimmune hepatitis (AIH): including positive anti-mitochondrial antibody (22.8 U, normal range 0-20), positive F-actin (72 U with normal 0-19), and positive anti-smooth muscle IgG (1:40 titer with normal <1:20). An outpatient liver biopsy was arranged, but the patient did not attend the procedure and later endorsed fear of having another biopsy. Given his possible diagnosis of AIH, a thiopurine methyltransferase level (TPMT) level was checked (within normal limits) and subsequently steroid-sparing immunosuppression was initiated with azathioprine. He was maintained on hydroxychloroquine and prednisone was tapered.

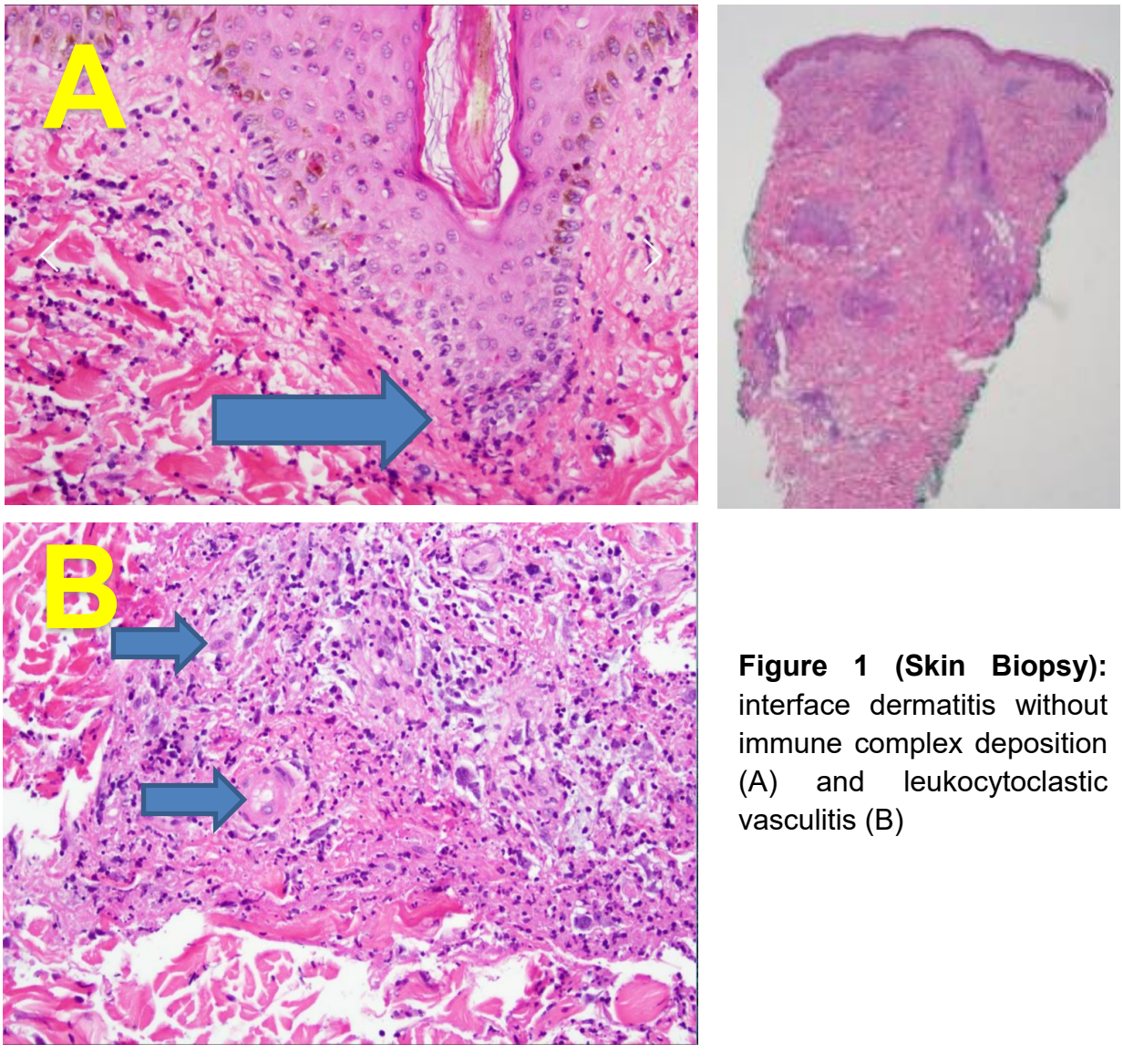

Figure 1 (Skin Biopsy): interface dermatitis without immune complex deposition (A) and leukocytoclastic vasculitis (B)

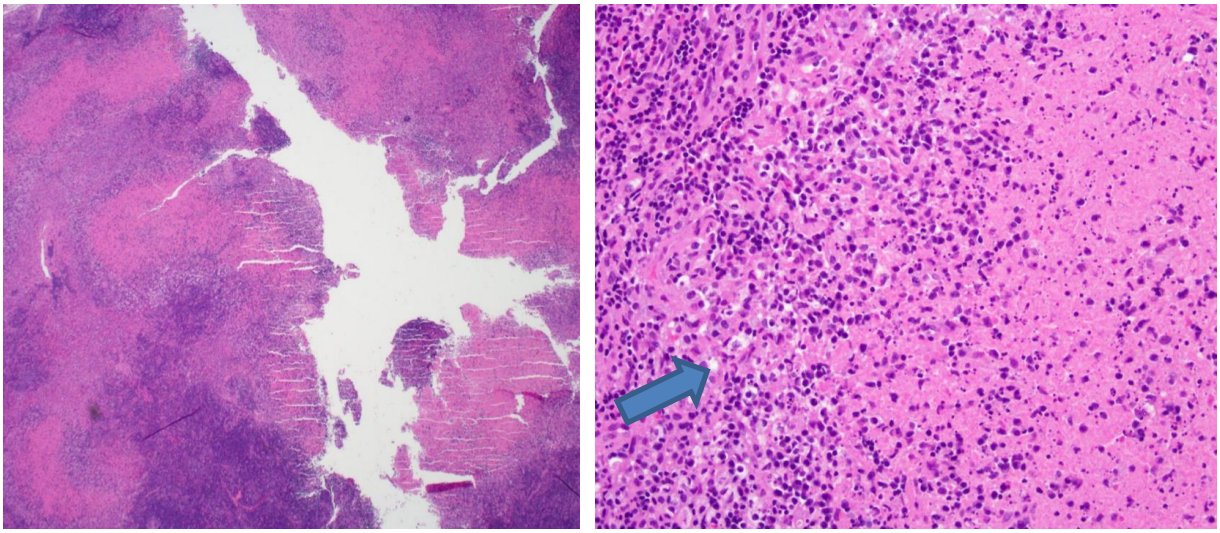

Figure 2. Lymph Node Biopsy. Necrosis with palisading foamy macrophages and notably, absence of neutrophils.

Table 1: CSF Analysis from Lumbar Puncture

CSF Studies	Results
GLUCOSE	56 mg/dL
PROTEIN	55.2 mg/dL (H)
LYMPHOCYTES	85%
MONOCYTES/MACROPHAGES	3%
NEUTROPHILS	1%
NUCLEATED CELLS	13 (H)
RED BLOOD CELLS	2
XANTHOCHROMIA	Absent

Discussion

Kakuchi-Fujimoto Disease (KFD) or histiocytic necrotizing lymphadenitis was originally reported in 1972 in Japan and is characterized by self-limiting lymphadenopathy[1], accompanied by fever and leukopenia in up to 50% of cases[2]. It is typically seen in patients under the age of 30 with a female to male predominance of 4:1[2 3]. The hallmark of Kakuchi-Fujimoto Disease is cervical lymphadenopathy, which is usually tender to palpation. Cervical lymph nodes are most commonly affected (80% of patients) followed by axillary (14%) and supraclavicular (12%) according to one study[4]. Constitutional symptoms including fever, weight loss, sweats, and malaise are also common. Laboratory testing is non-specific but patients may have leukopenia (usually neutropenia), anemia, thrombocytopenia and elevated inflammatory markers (C-reactive protein and erythrocyte sedimentation rate). Atypical lymphocytes may also be seen on a peripheral blood smear.[5]

The origin of Kakuchi-Fujimoto Disease is unknown but a viral etiology has been hypothesized including Epstein-Barr virus, human herpes virus 6, rubella virus, parvovirus B19, varicella zoster, paromyxovirus and parainfluenza virus[4,6]. There has been some postulation of possible genetic predisposition

based on familial occurrence[6], but this has not been clearly elucidated to date. Additionally, an autoimmune etiology has been suggested due to cases in which SLE is diagnosed in association with Kakuchi-Fujimoto Disease. A review of 244 cases of Kakuchi-Fujimoto Disease in the literature by Kucukardali found 32 cases (13%) were associated with systemic lupus erythematosus[3]. A subsequent literature review described three patterns of presentation including KFD before the onset of SLE (30%), simultaneous occurrence of both disorders (47%) and KFD after SLE diagnosis (23%)[5]. Given this association, it is important to be aware of the possibility of these diagnoses occurring contemporaneously. It is important to further understand the overlap of SLE and KFD to better understand disease outcomes and treatment strategies when these diseases occur simultaneously. However, given diffuse lymphadenopathy is not uncommon in lupus and lymph nodes are often not biopsied, the lymph node abnormalities described may be more common than we currently recognize and is a potential limitation of interpreting KFD in this particular case.

Our patient presented with elevated transaminases and positive autoimmune hepatitis serologies (specifically anti-mitochondrial, anti-F-actin and anti-smooth muscle antibodies). Hepatic involvement as a manifestation of Kakuchi-Fujimoto Disease has been reported in the literature. A review of 58 patients in Taiwan with Kakuchi-Fujimoto Disease found liver function impairment (defined as ALT > 40 U/L) in 14% of patients[4], and another review found elevated ALT in 23.3% and elevated alkaline phosphatase in 22.7%[7]. Interestingly, our case is only the second reported in the literature of Kakuchi-Fujimoto Disease presenting in association with autoimmune hepatitis. It is also the first documented case, to our knowledge, to present specifically in association with positive F-actin and anti-mitochondrial antibodies. The only other case reported in the literature is a 17 year old who presented with cervical adenopathy with pathology demonstrating KFD, elevation of transaminases and positive anti-smooth muscle antibodies at 1:320 titer[8]. It is important for clinicians to be aware of the potential association with autoimmune hepatitis in patients with KFD and liver involvement, particularly since this may affect the immunosuppressive agent selected (for instance, azathioprine which is frequently used for treatment of both SLE and autoimmune hepatitis was chosen for this patient).

Diagnosis of KFD can be difficult given its clinical presentation and large differential diagnosis, and has been frequently misdiagnosed as malignant lymphoma or tuberculous lymphadenitis[3]. Ultimately, the definitive diagnosis is based on histopathology of biopsied lymph nodes, characterized by focal necrosis in cortical and paracortical areas surrounded by crescentic histiocytes, and importantly, absence of neutrophils[5]. This necrotizing lymphadenitis without neutrophils can be seen in either KFD or SLE-related lymphadenitis. KFD can be differentiated from lupus lymphadenitis pathologically by the absence of plasma cells and hematoxylin bodies within the lesions[6].

While most patients with KFD have a self-limited course with spontaneous resolution, there is a minority of patients with documented progression to systemic lupus erythematosus[7]. Specifically, patients with KFD who have elevated levels of ANA antibodies at diagnosis can later progress to develop autoimmune diseases such as SLE[7]. While most cases of KFD are associated with clinical resolution, there can be significant morbidity in some patients. For example, there have been reports of death in patients with KFD and SLE due to severe infections and development of hemophagocytic syndrome[5 6]. It is important to recognize the association of lupus with KFD, since these comorbidities in tandem can lead to a more aggressive course and should be treated and monitored to prevent long-term sequelae. Our patient presented with encephalopathy and given neurologic

symptoms are not reported commonly with KFD, it is possible these were neuropsychologic manifestations of SLE, again emphasizing the importance of recognizing this association, and continued close monitoring of the patient. Additionally, patients with positive autoantibodies not otherwise diagnosed with SLE should be screened and monitored for subsequent development of concomitant autoimmune disease.

(1) Ethics approval

Our institution does not require ethical approval for reporting individual cases or case series.

(2) Informed consent

Verbal informed consent was obtained from the patient(s) for their anonymized information to be published in this article.

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